

Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 39-47, 49-51 are pending in this application. Claims 39-43 and 50-51 remain rejected. Claims 44-47 and 49 have been allowed. With the foregoing amendments, Claims 50-51 now depend on allowed Claim 44 and should be allowable. The rejections to the remaining claims are respectfully traversed.

Claim Rejections – 35 USC § 112, First Paragraph, Enablement

Claims 39-43, 50 and 51 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The rejection has two parts.

First, the Examiner has acknowledged that the specification is enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO: 292 or the mature form thereof, having the activity of inhibiting VEGF-stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells, but has found that other variants of SEQ ID NO: 292 are not enabled. According to the rejection, "[i]t is highly unlikely that the extracellular domain alone would test positive in any of the assays described..."

Second, changing her earlier assessment of this issue, the Examiner has determined that Assay 64 (Skin Vascular Permeability Assay) "does not provide the skilled artisan with guidance for how to use the claimed polypeptides." In support of this conclusion, citing Barsoun et al. and Szalai et al., the Examiner notes that "the skilled artisan would conclude that a positive result in this assay indicates that the polypeptide is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic."

Applicants disagree with and respectfully traverse both parts of the rejection.

With regard to the assertion that it is unlikely that the extracellular domain alone would test positive in any of the relevant biological assays, Applicants note that the burden is on the Examiner to support all rejections with valid scientific reasoning and/or scientific evidence. Only after the Examiner has made this threshold showing does the

burden of rebuttal shift to Applicants. In the present case, the Examiner has failed to advance any scientific arguments or evidence in support of her position, therefore, a *prima facie* case of lack of enablement on this ground has not been established. Nonetheless, Applicants note that the extracellular domain (soluble form) of polypeptides is typically known to share the biological activity of the mature full-length polypeptide. Thus, for example, the extracellular domains of cell adhesion molecules, CD4, etc. are known to be biologically active in isolated form, and as part of immunoadhesins, where the extracellular domain is fused to an immunoglobulin heavy chain constant region sequence.

Applicants also strongly disagree with the Examiner's suggestion that the observed inflammation in Assay 64 is due to a hypersensitivity response, and submit that PRO331-associated inflammation cannot be equated to the effect of an "irritant." A reaction to an 'irritant or foreign substance' produces a hypersensitive reaction in a presensitized animal. That is, injection of an antigen or foreign substance intradermally or subcutaneously into an animal with high levels of circulating antibodies specific for that irritant/antigen leads to formation of localized immune complexes, which mediates an acute Arthus reaction or an inflammatory reaction within 4-8 h. Applicants submit that the types of assays and hence, the responses observed in each of the references cited by the Examiner are in no way similar to Assay 64. Barsoun injected mice subcutaneously twice for 7 days before challenging the animal with the allergen, which resulted in a delayed-hypersensitive reaction. Szalai teaches an *in vivo* model for the Arthus reaction (RPA reaction) where excess antibody is injected into rabbit skin previously infused intravenously with the corresponding antigen (see column 1, lines 1-5). Such hypersensitive-inflammatory responses occur due to IgE-mediated mast-cell activation which release short-lived mediators like histamines and prostaglandins. These hypersensitive and the Arthus reaction assays in the cited references are absolutely different from the skin vascular permeability assay (Assay 64) in that there is prior pre-sensitization with the corresponding antigen for inflammation to occur.

On the contrary, well-known proinflammatory molecules like the cytokine IL-8, histamine, prostaglandins, etc., as well as the claimed molecule, PRO331, produce inflammatory reactions in non-presensitized animals, which is neutrophil-mediated (See Rampart submitted in previous IDS, column 1, Abstract that states that a proinflammatory molecule is characterized by:

"fast onset of neutrophil accumulation, short duration (half-life of 60-70 min) and parallel plasma leakage"). PRO331 showed inflammatory response and accumulation of neutrophilic, eosinophilic, monocytic or lymphocytic cells within 6 hr (fast onset) in Assay 64. If, as suggested by the Examiner, PRO331 were an allergen/ irritant, there should not have been any accumulation of neutrophils during the immediate short phase of the reaction, since immediate allergy-associated inflammation is mast cell-mediated and is not neutrophil-mediated. Instead, the involvement of neutrophils clearly demonstrates that PRO331 meets the criteria of a proinflammatory molecule and not that of an allergen. Thus, from the "skin vascular permeability" assay results, Applicants correctly concluded that PRO331 is a proinflammatory molecule.

Applicants submit that PRO331's utility lies in its use as a target for the development of anti-inflammatory agents (as is routinely done with other inflammatory molecules like prostaglandins, endothelins). From the data disclosed in the specification, specifically in the skin vascular permeability assay, the skilled artisan would know that PRO331 is a proinflammatory molecule that attracts neutrophils besides other immune cells. Hence, they would know that anti-PRO331 would be useful against inflammations that involve immune cells like neutrophils (which include acute inflammations such as lung and renal inflammation, bacterial infections, etc.) without undue experimentation. Applicants submit that based on the guidance in the present disclosure, the existing knowledge in the art at the time of filing which was very high, and the level of skill of the artisan in the field of anti-inflammatory therapeutics, the skilled artisan would know precisely how to make and use PRO331 and anti-PRO331 against inflammation.

In conclusion, Applicants submit that the reasoning underlying the present rejection is invalid on both grounds. Therefore, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C44). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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